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Focus on

Position paper of French Interventional Group (GACI) for TAVI in France in 2018

Position paper du GACI sur le TAVI en France en 2018

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Abstract

Aortic stenosis is a frequent disease in the elderly. Its prevalence is 0.4% with a sharp increase after the age of 65, and its outcome is very poor when the patient becomes symptomatic. The interventional procedure known as TAVI (trans-catheter aortic valve implantation), which was developed in France and carried out for the first time in Rouen by Prof. Alain Cribier and his team in 2002, has proven to be a valid alternative to surgical aortic valve replacement. At first, this technique was shown to be efficient in patients with contra-indications to surgical treatment or deemed to be at high surgical risk. Given the very promising outcomes achieved as a result of close heart team collaboration, appropriate patient selection, simplified procedures and reduced complication rates, transfemoral (TF) TAVI is now preferred in symptomatic intermediate risk patients > 75 years old according to the latest ESC guidelines. In 2017, in France, TAVI is currently performed in 50 centers with on-site cardiac surgery. The 2016 TAVI outcomes recorded in the French national TAVI registry (France TAVI) are very encouraging and show that for 7133 patients treated (age 83.4 ± 7 years, logistic Euroscore 14%), 87% of whom via the TF approach, cross-over to surgery was very low (0.5%) with a 3.0% in-hospital mortality rate. The substantial increase in TAVI indications and the improvement of its outcomes may in the near future call for a reconsideration of the number of high volume centers authorized to carry out this technique.

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Keywords: TAVI; Aortic stenosis; France; Aortic bioprotheses

Résumé

Le rétrécissement aortique est une pathologie fréquente chez le sujet âgé. La prévalence de cette pathologie dans la population générale est de 0,4 % et son pronostic est sombre dès que le patient devient symptomatique. La procédure de mise en place d'une valve aortique

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par voie percutanée (Transcatheter Aortic Valve Implantation: TAVI) s'est très rapidement développée après le premier cas réalisé à Rouen par le Pr Cribier et son équipe en 2002, comme une alternative efficace à la chirurgie de remplacement valvulaire aortique. Dans un premier temps, cette technique a démontré son efficacité, pour les patients contre-indiqués pour la chirurgie et à haut risque chirurgical. Du fait de résultats très encourageants, liés à un travail en *heart team*, une sélection efficace des patients, des procédures simplifiées avec de moins en moins de complications, les indications du TAVI se sont progressivement étendues aux patients âgés de plus de 75 ans à risque intermédiaire selon les derniers guidelines de l'ESC. En 2017, en France, 50 centres réalisent des TAVI, avec une moyenne de 180–200 procédures par an. Les résultats obtenus dans le registre national France TAVI sont très encourageants avec en 2016, pour 7133 patients traités, dont 86,7 % par voie trans-fémorale, un taux de conversion chirurgicale de 0,5 % et une mortalité hospitalière de 3,0 % chez des patients âgés en moyenne de 83 ans. L'élargissement des indications de TAVI dans les années à venir et l'amélioration des résultats de cette technique devront faire rediscuter le nombre de centres autorisés à réaliser cette technique.

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Mots clés : TAVI ; Sténose aortique ; Bioprothèse aortique

1. Introduction

Aortic stenosis (AS) is frequent in the elderly and associated with very poor outcomes in symptomatic patients. Transcatheter aortic valve implantation (TAVI) has proven to be a valid alternative to surgical aortic valve replacement in contraindicated, high risk and intermediate risk patients. In France, where this technique was first developed, substantial experience has been acquired leading to gradual procedural simplification. The goal of this consensus paper is to describe the current status of TAVI procedures in France and to prepare the future of this technique.

2. Physiopathology and epidemiology

AS is the most severe presentation of calcific aortic disease and is characterized by fibro-calcific remodelling. Valvular remodelling begins with lipoprotein deposition and chronic inflammation, leading to osteogenic differentiation of valve interstitial cells and active leaflet calcification [1]. Despite common features with atherosclerosis, no pharmacological intervention has been shown to slow down AS progression [1].

Large population-based studies have reported consistent estimation of annual AS incidence rates of 0.36 and 0.37 per 1000 for patients managed in hospital [2,3]. In the general population, incidence rates are higher (4.9 per 1000) when based on systematic echocardiographic screening [4].

The prevalence of AS has been estimated to be 0.4% in the general population and 1.3–1.7% in patients aged over 65 in developed countries [5,6]. Prevalence of AS markedly increases after the age of 65 and is estimated at 3.4% for severe AS after the age of 75, 75% of patients being symptomatic [1,7]. The natural history of severe, symptomatic AS is particularly poor, with 5-year mortality of 60% after a first hospitalization [3]. Mortality is higher after heart failure or in octogenarians with comorbidities [8].

Reliable epidemiologic data in heart valve disease have important implications for planning healthcare resources. The number of patients with AS is expected to increase threefold in the next 50 years due to the lack of prevention strategies and population ageing [8].

3. History of TAVI

The development of TAVI has been a long odyssey since its conception in the early 1990s in order to offer a less invasive therapeutic option to patients with AS deemed ineligible for surgical treatment.

The story began in 1985 in Rouen when Alain Cribier initiated the balloon aortic dilatation technique.

Following an international surge of enthusiasm for the technique, its limitations, especially the occurrence of early valvular restenosis, prompted him to design the concept of the 'percutaneous aortic valve'.

The start-up company, called 'Percutaneous Valve Technologies' allowed the development and animal testing of the first balloon-expandable prostheses in 2000, before the first in-man implantation at the University Hospital of Rouen (France) on April 16, 2002 [9]. The acquisition of the start-up company by Edwards in 2004 led to significant technological enhancements, while another competing self-expandable prosthesis, the Medtronic Corevalve, emerged two years later. Multiple randomized trials and registries evaluating these two devices have contributed to the extraordinary expansion of TAVI, as well as its inclusion in the European and US guidelines since 2012 and 2014, respectively, and the recent extension of indications in patients at intermediate risk in 2017 [10].

3.1. Patient evaluation before TAVI

Evaluation and patient selection are key steps before TAVI and should involve the heart team including cardiologists, imaging specialists, cardiac surgeons, anesthesiologists and, if needed, geriatricians or other organ specialists. Currently, in France, indication of TAVI is still limited to symptomatic patients with severe AS and contraindications for surgery or those considered high risk by the heart team.

The screening evaluation before TAVI should include (Table 1):

- echocardiography to confirm the severity of AS, to analyze the aortic valve morphology, the ascending aorta, the left ventricle

Table 1
Routine investigations before TAVI procedure.

Heart team evaluation	Always required
Geriatric evaluation	Frequently required
MSCT	Always required
Trans thoracic echocardiography	Always required
With measurement of PAPS and LV EF	
Trans esophageal echocardiography	For annulus measurement if MSCT failure
Coronary angiography	Always required
Supra aortic vessels ultrasonography	Always required
Dental check for infectious foci	Usually required

MSCT: multislice computed tomography.

(LV) dimension and function, to exclude dynamic ventricular obstruction and evaluate the mitral valve;

- coronary angiography to guide decisions of revascularization;
- multislice computed tomography (MSCT) is essential for decision-making particularly for selection of the best access route in terms of minimal vessel size, tortuosity and calcifications.

For femoral access the ratio between the external diameter of the sheath and the minimal vessel diameter should be <1.1 in the absence of calcifications [11]. When femoral access is not possible, MSCT may assess the feasibility of an alternative access route (trans-carotid, trans-aortic, subclavian or trans-apical). In addition, with regard to the sizing and selection of the valve type, MSCT is now the gold standard for assessing the horizontal and ascending aorta, the size of the sinus of valsalva, the aortic annulus size and shape, the amount of calcification, the bi or tricuspid nature of the valve, the distance between the annulus and coronary ostia, the presence of a septal bulge, the presence of calcifications in the outflow track, in order to select the most suitable prosthesis size and type and the optimal view for valve positioning.

For patients with CAD and severe AS undergoing TAVI, the optimal strategy with respect to completeness of revascularisation in TAVI patients should be evaluated by the *Heart Team* on a case-by-case basis, taking into consideration the extent and complexity of CAD, the myocardium at risk and the anticipated complexity of PCI, as well as the comorbidities of each individual patient. Of note, the recently published ESC guidelines on myocardial revascularisation recommend PCI in CAD patients undergoing TAVI with a diameter stenosis $>70\%$ in proximal coronary segments [10]. As it relates to the timing of revascularisation, both staged PCI followed by TAVI and concomitant PCI and TAVI represent valid strategies with advantages and disadvantages that need to be carefully weighed on an individual basis [12].

Table 2
Specific subsets.

<i>Bicuspid aortic valve</i>
Bicuspid anatomy should not be excluded from TAVI. However, it must be carefully discussed based on patient-specific aortic root anatomy and calcium distribution assessed with MSCT
<i>Degenerated surgical bioprostheses</i>
TAVI is now considered only in high-risk patients, but may become the preferred treatment for surgical bioprosthesis valve failure
<i>Pure aortic regurgitation</i>
To date, the role of TAVI for native aortic regurgitation treatment is marginal and has consisted mainly of “off-label” application in very high-risk patients

4. Indications of TAVI

For many years surgical aortic valve replacement (SAVR) has been the treatment of choice for the majority of patients with severe AS, resulting in relief of symptoms and improved survival. Over the last 15 years, $>400,000$ TAVI procedures have been performed in >75 countries and TAVI is now a mature technique, with a standardized and predictable procedure and outcome.

In September 2017, based on the accumulation of randomized data in high and intermediate risk patients, the updated ESC guidelines [10] gave a clear indication for SAVR for symptomatic AS in low-risk patients (I-B), while TF TAVI should be preferred according to the heart team discussion in patients >75 years with an STS $\geq 4\%$ or EuroSCORE II $\geq 10\%$, and also in cases of hostile thorax, previous cardiac surgery, poor mobility, severe comorbidity, frailty, risk of mismatch (I-B). TAVI should only be performed in hospitals with on-site cardiac surgery. Specific subsets for TAVI are listed in Table 2.

Valve durability is presently good with a superior valve area at 5 years in the TAVI group compared to surgery [13], but very few data are available beyond 5 years [14].

For patients with bicuspid aortic valve (BAV), no significant differences were found in clinical outcomes of patients undergoing TAVI [15,16]. Although the use of TAVI in patients with BAV is increasing, TAVI in patients with BAV must be carefully discussed with the heart team. The reasons for this lie in theoretical concerns regarding the elliptical shape of leaflet opening in BAV together with a possible asymmetric distribution of calcification [15,16]. Accordingly, patients with known BAV have been excluded from TAVI clinical trials, or are younger patients with low surgical risk.

5. TAVI procedure and simplified TAVI

In less than 15 years, TAVI has become a mature and very standardized technique with a low risk of complications. For the TF approach, selection of the side and precise location of the puncture should be based on careful reading of the MSCT images of the vascular axes. Angiographic and femoral ultrasound can also be helpful for finding the optimal puncture site. Careful reading of the MSCT scan prior to the procedure is crucial for optimal valve selection (type and size) and implantation

strategy (predilatation or not). MSCT can also be used for selection of the optimal working view in order to reduce the amount of contrast media during the procedure. When implementing the TF approach, it is preferable to have two operators (at least one interventional cardiologist). The presence of an anesthetist is better in the cathlab to perform a conscious sedation with local anesthesia. It is also recommended that a pericardial drainage kit and a peripheral toolbox be immediately available.

A venous access of appropriate caliber is put in place and the patient receives light sedation with short half-life morphinic agents. The procedure is subsequently carried out under local anesthesia. After angiographic or ultrasound guided femoral puncture, a pre-closing technique using either double-suture Proglide or the Prostar suture is implemented under local anesthesia before sheath placement. In general, once the sheath is in place, a heparin injection ensures efficient anticoagulation with subsequent ACT monitoring in order to obtain an ACT superior to 250.

The secondary route allows contrast injection in the vascular axes as well as aortography during the TAVI procedure. The contralateral femoral access can be used as a secondary route, but the left or right radial approach is increasingly used. This allows a significant reduction in the rate of vascular complications, which are frequently observed in elderly patients undergoing transfemoral access [17,18]. It is recommended that a 6F long sheath be used for the transradial (TRA) access in order to minimize friction. The operator should ensure that all the appropriate equipment (balloons and stents) is available to perform TRA femoral angioplasty and stenting if necessary.

Due to the frequent impairment of renal function, the volume of contrast medium used during the procedure can be reduced by diluting it with 20% saline.

Temporary pacing required during valve deployment is performed by means of a pacing catheter placed in the right ventricle via venous femoral or brachial access or by using the guide wire positioned in the LV for valve delivery as described by Faurie et al. [19]. This technique obviates the need for placement of an electro-systolic pacing catheter in the right ventricle, thus reducing the rate of complications associated with the venous access as well as the rate of right ventricular perforation, which is not a rare occurrence. Pacing is carried out by using an alligator clamp positioned on the distal segment of a stiff 0.35' wire in front of the valve (cathode). The anode, also using an alligator clamp, is on a subcutaneous needle next to the femoral puncture site [19].

Pacing is performed at 180/min or higher in order to achieve a drop below 50 mmHg in arterial pressure during S3 valve deployment. It should be used also for pre or post dilatation, and as necessary in case of instability during Corevalve deployment.

Predilatation of the aortic valve using an appropriate balloon is recommended in patients with very calcified valves. Direct implantation of the valve without balloon predilatation is increasingly being performed in patients with moderately calcified valves on MSCT scan. This strategy has been associated in observational studies with favorable outcomes in terms of stroke, valve embolization, coronary occlusion or annulus rupture and is currently the subject of an ongoing randomized study.

The implantation technique depends on the type of valve used. Aortography is performed in the predetermined view in order to determine the position of the valve in relation to the aortic annulus. After the valve has been positioned and deployed, transthoracic echocardiography is the best way to identify significant para valvular leak (PVL), residual gradient and potential pericardial effusion. After removal of the wire, a final aortography should be carried out if possible, in order to check valve position, residual PVL and potential compromise of the coronary arteries' ostia.

After femoral closure, a post deployment contrast injection through the secondary vascular access is advisable in order to check the patency of the vascular suture as well as the absence of vascular complications. Certain teams recommend heparin neutralization (half or full dosage) at the end of the procedure at the time of vascular closure.

Conduction abnormalities should be assessed after valve deployment (lengthening of the PR interval, widening of the QRS interval and high degree conduction disorders) in order to determine the need for initiation or continuation of electro-systolic pacing or even pacemaker implantation. The electro-systolic pacing catheter can be positioned via the basilic approach (earlier mobilisation of the patient) or the femoral approach.

In patients with no coronary stenting, a dual antiplatelet therapy (aspirin and clopidogrel) is prescribed for 1 to 3 months followed by single therapy with aspirin or clopidogrel. A single antiplatelet therapy has been recently proposed by the ESC guidelines for patients at high risk of bleeding. Patients on previous oral anticoagulants or with a new occurrence of atrial fibrillation are discharged on anticoagulant treatment only or a combination of anticoagulant and single antiplatelet therapy. For patients with recent coronary stenting, the antithrombotic treatment is "à la carte" depending on the thrombotic and hemorrhagic risk. Optimal post TAVI anti-thrombotic treatment and, more specifically, the potential interest of non-vitamin K antagonist oral anticoagulant (NOAC) are still subjects of controversy. Several randomized trials are currently being conducted on this topic (POPULAR TAVI, ATLANTIS, GALILEO. . .).

6. TAVI devices

The main concept of the TAVI devices is based on a tricuspid pericardial leaflet prosthesis sewn within a metallic frame. This frame can be balloon-expandable (Sapien) self-expanded (Evolut R, Accurate Symetis, Portico, Centera) or mechanically expanded (Lotus) [20].

The leaflets are located at the previous annulus level (Sapien, Portico, Lotus) or in a supra-annular position (Evolut R, Symetis) with a positive impact on hemodynamic performances in small annuli.

Various solutions are used to facilitate access with the delivery device through small vessels, the common concept being the dissociation between prosthetic leaflets and the bulkiest part of the frame: late sliding of the balloon (Sapien) or prosthesis (Lotus) or supra-annular insertion. Recapture until almost full

release is possible for Evolut R and the Portico self-expanding valve, as well as for Lotus (recalled for the moment).

Radial strength of the frame at annulus level is a major feature that influences positively the apposition and the risk of PVL and negatively the risk of conduction disturbances [21]. Previous studies have yielded conflicting results regarding the role of the cover index (ratio valve diameter/annulus diameter) and depth of insertion on both the PVL and PM rates.

The use of an external skirt around the bottom of the frame is becoming popular (Sapien 3, Evolut R Pro, Accurate Neo, Lotus) in order to improve apposition without increasing the radial force. The impact on the rate of new PM remains unclear whereas the effect on PVL is certain.

The height of the frame is responsible for possible interactions with the coronary arteries' ostia particularly when take-off is low. All the frames, except the Lotus, have been designed to allow further access to coronary arteries for secondary interventions. Self-expanding frames extend into the ascending aorta, above the sino-tubular junction, to help the self-centering of the device.

The pericardial nature of the leaflets (bovine for Sapien and Lotus, otherwise porcine) is directly linked to previous experience with surgical bioprostheses. For this reason, the valve is stored in a liquid milieu and needs specific measures to be loaded by trained operators onto the delivery device at the time of the implantation. Some devices received anti-calcification preventive treatment. In the near future, some devices will be packed "ready to be used".

The complexity of the delivery devices, the handmade suturing of the pericardium and the training process of the operators explain the higher cost of TAVI prostheses in comparison with surgical valves; however, the rapid expansion of TAVI should have a beneficial impact on costs.

7. TAVI Complications and management

Over the past few years, TAVI procedures have become safer [22] and their associated risk of complications (Table 3) has steadily declined [23] thanks to rapid technological developments and refinements in TAVI devices as well as enhanced

pre-procedural imaging, improved patient selection and increasing operator experience.

However, patients experiencing severe TAVI complications that cannot be managed via an interventional approach may have to undergo emergent cardiac surgery, which is associated with a 50% in-hospital mortality rate [24,25].

Permanent pacemaker (PPM) insertion rates after TAVI (for the 2 major valve types, the Edwards SAPIEN balloon-expandable valve and the Medtronic self-expanding CoreValve) range from 2–9% and 9–42% respectively. Several studies have examined the incidence and potential mechanisms of conduction abnormalities associated with TAVI, new LBBB and CHB/high-grade AVB being the most common. Specifically, the use of the Medtronic self-expanding valves, larger valve sizes (particularly in patients with small aortic annuli), and greater valve implantation depth in the left ventricular tract, in addition to documented intraprocedural AVB, have all been associated with a higher risk of development of clinically significant conduction disturbances after TAVI. Despite this, there remain wide variations in practice regarding the monitoring of patients after TAVI for conduction abnormalities and the length of time temporary transvenous pacing leads remain in place after the procedure. There are no definitive practice guidelines addressing these issues. Patients must be monitored for at least 3 days, especially those who receive a self-expanding valve. The vast majority of conduction abnormalities leading to PPM insertion (88.8%) occurred either during or within 72 hours of TAVI [26]. Permanent pacemaker (PPM) insertion is indicated in the presence of a persistent LBBB > 160 ms and high-grade AVB.

Tamponade should be identified as soon as possible. Its most common cause [27] is right ventricular perforation related to a temporary pacemaker. Use of an LV wire for rapid pacing [19] may decrease this complication as well as femoral venous access complications. LV perforation related to the wire or delivery system can be prevented by optimal LV wire positioning, an appropriate distal wire curve, dedicated wires and perfect synchronization between the two operators.

Aortic annulus rupture is one of the most severe complications [28]. It can be prevented by optimal valve sizing. The use of a self-expandable valve is recommended in the presence of a calcium nodule in the anterior part of the annulus [11].

Ventricular fibrillation usually occurs in patients with a low potassium level and even more frequently when rapid pacing is needed for more than 20 seconds.

The risk of stroke is about 2%. The presence of debris in the ascending aorta, inadequate anticoagulation, renal impairment, repeated device implantation attempts, new-onset of atrial fibrillation have been shown to be associated with the occurrence of stroke [22]. The role of embolic protection devices is currently under evaluation [29].

Coronary obstruction occurs more frequently in women, in recipients of balloon-expandable valves and in patients undergoing valve-in-valve procedures [30]. Excluding patients with a lower-lying coronary ostium (< 10 mm) and shallow Valsalva sinus (< 30 mm) are key preventive measures [31]. One solution for preventing the occurrence of coronary obstruction is

Table 3
Main in-hospital complications of TAVI (from FRANCE TAVI).

Cardiac tamponade	< 5%
LV wire perforation	1–2%
Pace maker perforation	1–2%
Annulus rupture	< 1%
Aortic dissection	< 1%
Vascular complication	4–8%
Transfusion	4–15%
Severe aortic regurgitation	1–4%
Valve embolization	1–3%
Ventricular fibrillation	1–3%
Stroke	2%
Coronary obstruction	< 1%
Emergency cardiac surgery	0.7%
Acute kidney injury	5–15%

to deploy the valve using a guiding catheter and a protective coronary wire in the left or right coronary system [32].

Access site complications are the most frequent complications. They can be reduced by carrying out optimal evaluation of the ilio-femoral access. In the absence of calcification, a > 1.1 sheath size/minimal ilio-femoral size ratio has been shown to be associated with a high risk of severe femoral complications [33]. Selection of the puncture site is crucial and can be optimized using angio or echo guidance [34]. One-third of access site complications are related to the femoral contralateral approach and could, therefore, be eliminated by using the radial approach [35].

Aortic dissection mainly occurs during the transaortic approach learning phase and perforation in patients with a severely tortuous and diseased aorta.

Severe acute aortic regurgitation after predilatation is observed in 1–2% of cases. It is very important to have the percutaneous aortic valve ready when performing predilatation because hemodynamic collapse may occur very quickly. One option for avoiding this complication is valve implantation without predilatation.

Severe aortic regurgitation after valve deployment has become an unusual occurrence with the latest generation valves. It can be due to valve malpositioning, undersizing or severe valve or annular calcifications. The role of MSCT is crucial in order to select an optimal annulus perpendicular view, as well as the appropriate valve type and size. Undersizing with the Sapien 3 valve may be due to a preparation mistake or a leak between the inflator and the connection to the delivery system that should be systematically checked before introducing the valve into the sheath. In cases of malpositioning, deployment of a second valve is usually the best option. When the self-expandable valve is in the correct position, post dilatation with 1/1 valve/annulus ratio can be a good option for improving PVL.

Valve embolization is usually related to malpositioning or valve undersizing. The risk is increased in the presence of a septal bulge.

Acute kidney injury after TAVI can occur in these frail patients. Patient preparation is crucial (optimal hydration, removal of nephrotoxic agents, restricting the number of procedures requiring contrast media during a short period. Limiting the amount of contrast during the procedure (using MSCT for optimal view, dilution of contrast by 20%) and using the Angioguard [28] when the anticipated amount of contrast exceeds the creatinin clearance by a factor of 4 are the key preventive strategies.

8. Trans-catheter aortic valve implantation in France: current status

Trends in patients and procedural characteristics, as well as short-term outcomes of TAVI in France from 2010 to 2015 have been detailed recently [36]. In 2016 a total of 7133 patients were entered in the FRANCE TAVI database (5718 patients in 2015), confirming the considerable expansion of TAVI observed over the past few years. Patients treated in 2016 vs. 2013–2015 were the same age (83.4 years) and 51% were women (Table 3).

Logistic EuroSCORE continued to decrease with a median score of 14% in 2016 compared to 17% between 2013 and 2015 ($P=0.007$). The main differences in comorbidities observed between 2016 and 2013–2015 were a lower % of patients with prior coronary artery bypass graft (8.6% vs. 11.4%, $P<0.001$) and chronic pulmonary disease (17.8% vs. 20.2%), $P<0.001$.

Regarding the procedure (Table 4), the main findings were a dramatic decrease in the use of general anaesthesia (33.5% vs. 51.7%, $P<0.001$) and a modest increase in self-expandable valves implantation (39.7 vs. 34.9, $P<0.001$), probably reflecting the availability of the newest-generation CoreValve Evolut R device (Medtronic, Minneapolis, Minnesota) and the temporary interruption of Sapien 3 distribution in France at the end of 2016 by the company. The trans-femoral access was the standard of care accounting for 86.7% of procedures in 2016 with a low and stable rate of surgical conversion (0.5%). Of note, device success improved (97.7% vs. 96.8%, $P<0.001$).

Regarding outcomes (Table 5), in-hospital mortality decreased (3.0% vs. 4.4%, $P<0.001$). Notwithstanding a higher rate of missing data regarding in-hospital morbidity in 2016, which precludes definitive conclusions, reassuring trends were observed regarding the occurrence of valve migration (0.8% vs. 1.1%, $P=0.037$) and tamponade (1.5% vs. 2.0%, $P=0.012$) whereas stroke remained stable (2.0% of patients). Similarly, the need for a new permanent pacemaker remained unchanged (17.3% vs. 17.5%, $P=0.68$) as well as moderate or severe aortic regurgitation on discharge (9.9 vs. 10.2%, $P=0.62$). Finally, the median length of stay decreased from 8 to 7 days ($P<0.001$) (Table 6).

9. TAVI centers

In 2017, there were fifty TAVI centers in France (Fig. 1), each performing on average an annual volume of 180–200 TAVI procedures. By decree of July 3rd, 2012, the practice of TAVI is limited to centers meeting a set of criteria (Table 7), the most restrictive criterion being the requirement for on-site cardiac surgical activity in the same building. This framework is based on the need for rigorous patient selection during regular multidisciplinary meetings (Heart Team - ideally involving interventional cardiologists, cardiac surgeons, anesthetists and, when required, geriatricians or other organ specialists according to comorbidities) as well as the need for surgical conversion in the event of a complication. The need for on-site cardiac surgery is clearly established in the 2017 ESC guidelines.

Experience has shown that emergency surgical conversion during TAVI is rare (0.5% of all transfemoral procedures in 2016—according to the France TAVI registry), but this could be different when treating intermediate risk patients. In addition, evolving indications for TAVI have led to a steady increase in the number of TAVI procedures with a rise of almost 30% per year. Thus about 10,000 procedures were performed in 2017 and 20,000 procedures could have been performed if the intermediate risk were to be reimbursed in France. Therefore, the growing demand for undertaking TAVI could lead to changes in the criteria listed in Table 1, as well as an increase in the number of TAVI centers.

Table 4
Baseline characteristics of TAVI patients in the FRANCE TAVI registry.

Characteristics	FRANCE TAVI2016(n = 7133)	FRANCE TAVI2013–2015(n = 12804)	P value
<i>Clinical characteristics</i>			
Age, years	83.4 ± 6.9	83.4 ± 7.2	0.998
Male sex, n./total n. (%)	3504/7133 (49.1)	6314/12804 (49.3)	0.798
Logistic EuroSCORE, (mean ± SD)	17.6 ± 12.3 (n = 6845)	17.9 ± 12.3 (n = 12341)	0.007
Median (IQR)	14.0 (9.0–22.2)	15.0 (9.5–23.0)	<0.001
NYHA class III or IV, n./total n. (%)	4083/6651 (61.4)	8269/12241 (67.6)	<0.001
<i>Clinical history, n./total n. (%)</i>			
Previous CABG	601/6978 (8.6)	1441/12684 (11.4)	0.016
Previous SAVR	323/6960 (4.6)	559/12659 (4.4)	0.557
Atrial fibrillation	1281/5535 (23.1)	2763/11119 (24.9)	<0.001
Peripheral vascular disease	1597/6956 (23.0)	2853/12629 (22.6)	0.171
Chronic pulmonary disease	1236/6938 (17.8)	2551/12641 (20.2)	
Serum creatinine ≥ 200 µmol/L	326/6847 (4.8)	635/12178 (5.2)	<0.001
<i>Echocardiographic findings</i>			
Ejection fraction, %	56.5 ± 13.0 (n = 6671)	55.2 ± 13.6 (n = 12378)	<0.001
Median (IQR)	60 (50–65)	60 (45–65)	
Aortic valve area, cm ²	0.71 ± 0.25 (n = 6068)	0.69 ± 0.26 (n = 11569)	
Aortic mean gradient, mm Hg	47.4 ± 15.3 (n = 6674)	47.2 ± 15.9 (n = 12340)	0.241 0.014
Moderate or severe MR, n./total n. (%)	1291/5310 (24.3)	2369/10498 (22.6)	

Table 5
Procedural characteristics of TAVI patients (from FRANCE TAVI).

Characteristics	FRANCE TAVI 2016(n = 7133)	FRANCE TAVI2013–2015(n = 12804)	P value
General anesthesia, n./total n. (%)	2363/7059 (33.5)	6531/12645 (51.7)	<0.001
<i>Approach</i>			
Transfemoral, n (%)	6184/7133 (86.7)	10602/12804 (82.8)	<0.001
Transapical, n (%)	185/7133 (2.6)	541/12804 (4.2)	
Sub-clavian, n (%)	213/7133 (3.0)	385/12804 (3.0)	
Others, n (%)	551/7133 (7.7)	1276/12804 (10.0)	
<i>Valve type</i>			
Edwards SAPIEN, n (%) *	4279/7133 (60.0)	8232/12804 (64.3)	<0.001
Medtronic CoreValve, n (%)	2832/7133 (39.7)	4465/12804 (34.9)	
Others, n (%)	22/7133 (0.3)	107/12804 (0.8)	
Conversion to surgery, n./total n. (%)	30/6680 (0.5)	65/12557 (0.5)	0.519
Device success, n./total n. (%)	6940/7103 (97.7)	12139/12544 (96.8)	<0.001

Any future change in the undertaking of TAVI must, however, involve preservation of the absolute necessity for a formalized Heart Team meeting as well as a minimum TAVI case volume, considering the well-established relationship between institutional TAVI volume of activity and the clinical outcomes [37–45]. Finally, it is important to consider the requirement for vascular surgery and stroke management, given the frequency of vascular (6–8%) and neuro-vascular (2%) complications. In any case, a precise follow-up of all TAVI activity must be systematically undertaken, which is made possible by the requirement for TAVI centers to submit all TAVI cases to the French national registries.

10. TAVI in women

At present, a small number of registries have investigated gender-specific differences in outcomes after TAVI, reporting

variable results [46–49]. The available TAVI data show a greater proportion of women than in previous coronary clinical trials, in which the inclusion rate of female patients has historically been low. In the FRANCE 2 registry, 49% of participants were female. In the PARTNER trial, in the subgroup of patients at high surgical risk who were assigned to undergo TAVI, 42.2% were female; 39.3% of patients treated via a femoral approach were female, compared with 49% in the apical arm. Comorbidities differ between the sexes.

In a recent collaborative patient-level meta-analysis of 11,310 patients [47], median follow-up was 387 days (interquartile range, 192 to 730 days). The Kaplan-Meier survival curve showed a significant survival advantage for women (log-rank $P < 0.001$) (Fig. 2). The 1- and 2-year survival estimates were 82.7% (95% CI: 81.6%, 84.0%) and 74.0% (95% CI: 72.5%, 75.4%), respectively, for women and 78.2% (95% CI: 77.0%, 79.3%) and 67.8% (95% CI: 66.3, 69.3%), respectively, for men.

Table 6
In-hospital outcomes of TAVI patients (From FRANCE TAVI).

Outcomes	FRANCE TAVI 2016(n = 7133)	FRANCE TAVI2013–2015(n = 12804)	P value
<i>Time from implantation to discharge</i>	(n = 6842)	(n = 12672)	
<i>Median (IQR)</i>	7 (5–9)	8 (6–11)	<0.001
1–5 days	2242 (32.8)	3132 (24.7)	
6–9 days	3134 (45.8)	5744 (45.3)	
≥ 10 days	1466 (21.4)	3796 (30.0)	
<i>Complications, n./total n. (%)</i>			
All-cause Death	215/7133 (3.0)	562/12804 (4.4)	<0.001
Annulus rupture	22/6680 (0.3)	52/12557 (0.4)	0.366
Aortic dissection	16/6680 (0.2)	46/12557 (0.4)	0.140
Valve migration	53/6680 (0.8)	139/12557 (1.1)	0.037
Tamponade	102/6680 (1.5)	256/12557 (2.0)	0.012
Stroke	132/6680 (2.0)	249/12557 (2.0)	0.974
Permanent pacemaker implantation ^a	991/5744 (17.3)	1870/10681 (17.5)	0.681
<i>Echocardiographic findings</i>			
Aortic valve area, cm ²	1.83 ± 0.60 (n = 2420)	1.76 ± 0.56 (n = 4724)	<0.001
Aortic mean gradient, mm Hg	10.9 ± 6.3 (n = 5782)	10.3 ± 6.3 (n = 10684)	<0.001
Moderate or severe AR, n./total. (%)	580/5846 (9.9)	1119/11007 (10.2)	0.615

^a Numbers are given for patients without prior permanent pacemaker.

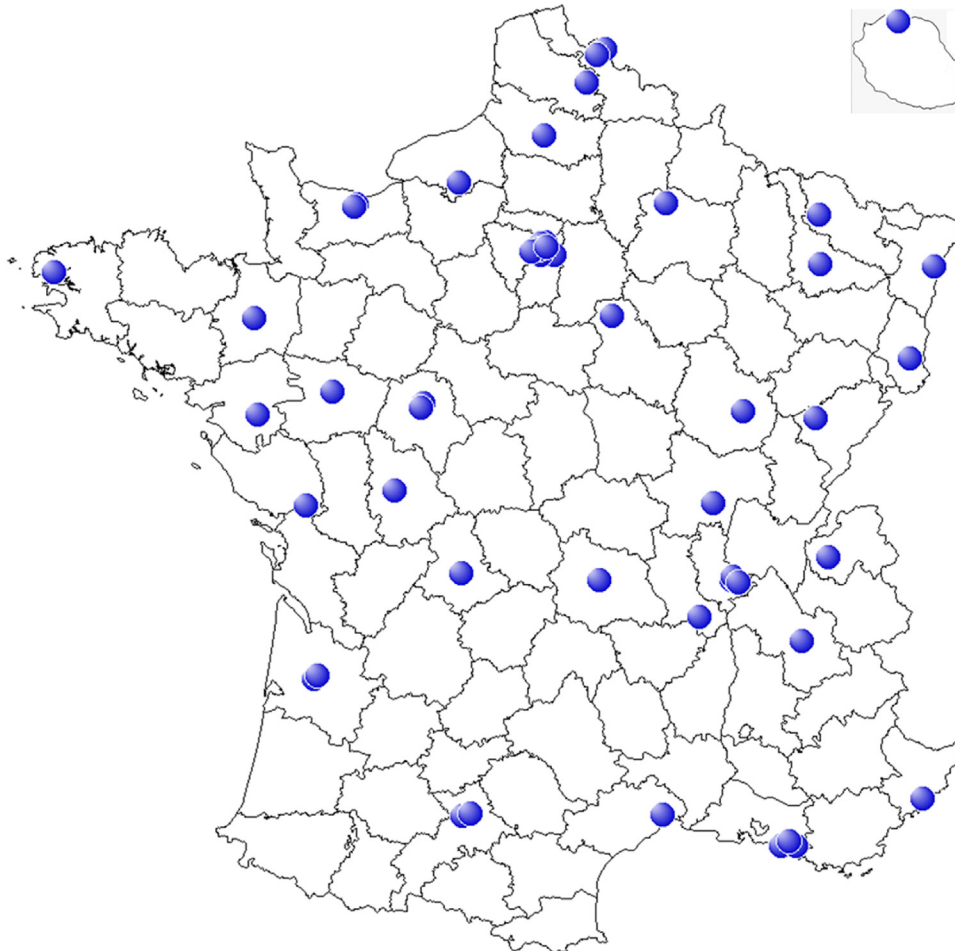


Fig. 1. TAVI Centers in France (2017).

In the Cox model for all-cause mortality, adjusted HR for female gender was 0.79 (95% CI: 0.73, 0.86; $P < 0.001$).

It is tempting to speculate that technical improvements in TAVI procedures, reduction in sheath and valve sizes and a

consequent decrease in vascular complications may further enhance the female advantage in outcomes.

Additional investigations into treatment disparities and long-term outcomes in women with severe AS treated by TAVI are

Table 7

Principal criteria for TAVI Centers according to the 3rd July 2012 document from the official journal of french republic).

On-site cardiac surgical activity

On-site interventional cardiology activity

Interventional cardiology and cardiac surgery are performed in the same building

The work flow enables the use of extracorporeal circulation

The health facility has a team comprised of at least one interventional cardiologist, a cardiothoracic surgeon, an anesthetist trained in cardiac surgery, an anesthesiology nurse and a cardiologist specialized in echocardiography. For transcatheter aortic (carotid, subclavian and femoral) arteries, the team may involve a vascular surgeon

The health facility has a Heart Team whose mission is to select patients along with the implantation technique during a formal multidisciplinary meeting involving at least

A non-interventional cardiologist

An interventional cardiologist

A cardiac surgeon

An anesthetist

In addition, this team may include a geriatrician

The health facility performs > 200 surgical aortic valve replacements during the twelve months prior to the placement of percutaneous aortic valvular bioprostheses

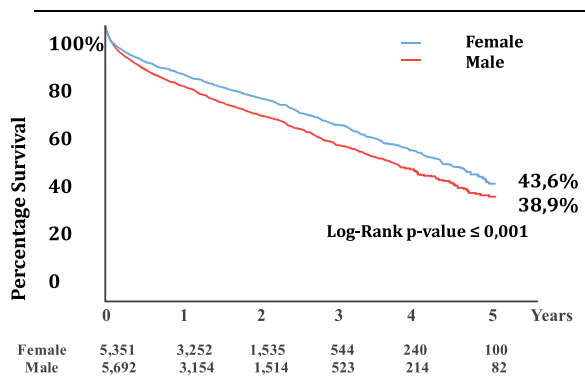


Fig. 2. Kaplan-Meier Plot of all-cause Mortality.

warranted, because the cost-effectiveness of TAVI procedures in women could be further increased by women's longer life expectancy.

11. TAVI in patient with atrial fibrillation

Atrial fibrillation and aortic valve stenosis are both elderly patients' pathologies, that have similar risk factors and increase with age [50]. Up to 40% of patients referred for TAVI may have chronic atrial fibrillation. It is well known that AF has a negative impact on surgical aortic valve replacement prognosis [51] and similarly it has been shown that pre-existing AF impairs the 1-year TAVI prognosis independently of procedural technical considerations [52]. New onset AF that occurs after a TAVI procedure while the rhythm was sinus beforehand has been described in 1 to 30% of procedures. It is associated with a greater 1-year risk of stroke and death and independently related to left atrial size and the surgical non femoral approach [52–54]. Thus, pre-existing or new onset AF are important predictors of 1-year mortality after TAVI, to the same extent as aortic regurgitation, and should be detected and treated with appropriate anticoagulation. The type of anticoagulant (i.e. new oral anticoagulants vs VKA) and the interest of a combination with antiplatelet agents are currently being tested in randomized control trials.

12. Conclusion

The efficacy of TAVI in the treatment of severe symptomatic AS has been clearly demonstrated. Heart team collaboration as well as simplification of the procedure and reduced complication rates has all contributed to improving TAVI's outcomes.

Given the considerable increase in TAVI indications which have been extended to include intermediate-risk patients, the number of TAVI centers in France will probably increase in the near future.

Disclosure of interest

Hakim Benamer: Proctoring for Edwards, Vincent Aufret: Received research grants from Edwards Lifescience and Medtronic. Bernard Chevalier: Proctoring for Medtronic. Helene Eltchaninoff: "lecture fees" Edwards Lifesciences. Thierry Lefèvre: Proctoring for Edwards, Proctoring for Abbott vascular. Guillaume Cayla, Philippe Commeau, Patrick Dupouy, Martine Gilard, Patrice Guerin, Bernard Iung, René Koning, Jacques Monsegu, Pierre Lantelme, Hervé Le Breton, Jean-philippe Verhoye, Pascal Motreff declare that they have no competing interest.

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